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EXAMINER

WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 05/09/2002

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/528,742	ROBEN ET AL.
	Examiner	Art Unit
	Joseph Woitach	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 22 February 2002.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-55 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-55 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

 If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

 a) All b) Some * c) None of:

 1. Certified copies of the priority documents have been received.

 2. Certified copies of the priority documents have been received in Application No. _____.

 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

 * See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

 a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.

4) Interview Summary (PTO-413) Paper No(s). _____.

5) Notice of Informal Patent Application (PTO-152)

6) Other: _____.

DETAILED ACTION

This application filed March 20, 2000, claims benefit to provisional application 60/139,579, filed June 17, 1999.

Applicants amendment, filed February 22, 2002, paper number 12, has been received and entered. Claim 55 has been amended. Claims 1-55 are pending.

Election/Restriction

Applicant's election with traverse of species: (a) a sulfo-NHS ester moiety ; (b) a biotin binding domain; and (c) dithiopropionate as the cleavable moiety in Paper Nos. 10 and 12 is acknowledged. The traversal is on the ground(s) that it would not constitute an undue searching burden on the Examiner because the Examiner could search the core concept of the invention encompassed by all 55 claims (see paper number 10, bridging pages 2-3). Applicants' arguments have been fully considered, but not found persuasive. This is not found persuasive because examination of the claims requires searching each of the specific species recited or taught in the instant disclosure encompassed by the pending claims, not a general review of concept encompassed by the claims. For anticipation and obvious-type rejections each and every element must be disclosed in a reference for the rejection to be proper. In the instant case, the number of various combinations of chemical moieties encompassed by the claims is very large. Each moiety must be searched and each possible combination would have to be accounted for a complete and proper rejection. With respect to a general art search for cross-linking compound,

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Examiner would concede that a review of the literature for a particular elected species may result in art for more than the elected species, however each possible combination of the moieties would have to be accounted for in the basis of the rejection. Therefore, it would constitute an undue search burden to examine all the possible species and combination of species encompassed by the claims.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-55 are pending. Claims 12, 14, 15, 31 and 33-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10. Claims 1-11, 13, 16-30, 32 and 36-55 are currently under examination as they are drawn to the elected species:(a) a sulfo-NHS ester moiety ; (b) a biotin binding domain; and (c) dithiopropionate.

Priority

It is noted that this application appears to claim subject matter disclosed in prior copending Application No. 60/139,579, filed June 17, 1999. A reference to the prior application must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application

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under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). Also, the current status of all nonprovisional parent applications referenced should be included.

Claim Objections

Claims 1, 11, 19, 30, 51, 52 and 55 are objected to because of the following informalities: The claims recite and/or encompass species which were not specifically elected. The claims should be amended to reflect the elected invention, specifically: the domains set forth as (a) a sulfo-NHS ester moiety ; (b) a biotin binding domain; and (c) dithiopropionate

Appropriate correction is required.

Specification

The disclosure is objected to because of the following informalities: The Brief Description of the Figures does not comply with 37 CFR 1.74. Specifically, a separate reference to and brief description of each of the drawing(s) must be present in the disclosure. Figure 3 has two panels, Fig 3A and Fig 3B which must be indicated in the figure legend.

In addition, the disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. For example, on page 14; line 25, a reference is made to the Pierce catalog. A review of the entire disclosure should be made for other embedded hyperlink, and appropriate correction made.

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Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 52-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The final Written Description Examination guidelines used in the basis of the rejection were published on January 5, 2001 (66 FR 1099), and are available at <http://www.uspto.gov/web/menu/current.html#register>.

In the instant case, the recitation of 'kit' and 'printed mater' lack adequate written description in the instant disclosure. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

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While the specification and the art provides adequate written description for the impermeable reagent comprising three domains, for the elected species: (a) a sulfo-NHS ester moiety ; (b) a biotin binding domain; and (c) dithiopropionate, as well as the other non-elected species, the specification fails to adequately describe the other necessary components of 'a kit' or the information contained in the 'printed matter' for practice of any of the claimed methods encompassed by the instant claims with particularity to indicate that Applicants had possession of the claimed invention. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics, Inc.*, 48 USPQ2d 1641, 1646 (1998). In the instant case, the specification indicates that a kit contains 'the cell impermeable reagents of the invention in suitable buffers for administration' and that it may 'also contain printed matter setting forth instructions for practicing the methods of the invention', however, the specification fails to specifically and clearly indicate what specific buffers are to be used or included, nor what other components would be contained in the kit besides the impermeable reagent. Further, the specification indicates that 'printed matter setting forth instructions' may also be included, however, the

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specification fails to indicate what the instructions are or provide an example of the specific instructions to be included (pages 20-21; bridging sentences). The reagents used in the instantly claimed methods are well known in the art, and the specification provides adequate guidance and written description for the reagents used in the instantly claimed methods. It is noted that the reagents are described broadly by the physical characteristics of each of the domains, however in view of the well known chemical and physical nature of the domains/components in the art, and the general recitation and listing of potential components comprised by each domain, the various and numerous combinations of the domains embodied by the impermeable reagent are clearly set forth. However, the intended use of the kit is specifically drawn to use in an intact organ and/or animal and the specification fails to clearly set forth the specific buffers and reagents, or provide specific instructions for the practice of each of the instantly claimed methods. The instant disclosure provides general guidance for the generation and use of impermeable reagents, however it fails to set forth the specific reagents or specific 'instructions' which would be specifically included in a kit. Further, it is noted that the instant claims recite several methods drawn to labeling and to isolating molecules exposed on the luminal surface of a cell without specifically setting forth any particular reagents or instructions to be included in a kit of any of the various methods. The skilled artisan cannot envision what the specific reagents are included in the kit or what the specific instructions recite, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention

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and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. In the instant case, while the disclosure may provide the general guidance to practice the instantly claimed methods, it fails to provide the specific details for each of the reagents to be included in a kit for practice of a particular method, and fails to set forth specific instructions for each of the methods which would be included in the written material.

Therefore, only the impermeable reagent to be included in a kit meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 17, 18, 20, 37 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, each of these dependent claims are drawn to

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identifying ‘an organ-specific or a tissue-specific molecule’ (claims 2 and 20) or more specifically a polypeptide (claims 17 and 37) and ‘a lipid or a carbohydrate’ (claims 18 and 38), however the instantly claimed method is drawn to the use of a first domain that ‘covalently and non-specifically’ binds a molecule on the luminal surface of a cell. The claims are unclear and/or incomplete because they fail to clearly set forth how a reagent which non-specifically binds to any molecule can identify an organ/tissue-specific molecule. Clearly setting forth in the claims the nature of the non-specific agent which specifically identifies an organ/tissue-specific molecule or providing additional steps wherein an organ/tissue molecule is defined would obviate the basis of this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 52 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Pierce Catalog & Handbook, 1994-95.

Claims 52 and 53 encompass a kit comprising a impermeable reagent comprising the three domains: (a) a sulfo-NHS ester moiety ; (b) a biotin binding domain; and (c)

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dithiopropionate and printed matter instructing for the use of the reagent. The instructions are being interpreted as providing the necessary guidance for the use of the reagent to react with the molecules present on the cell membrane. Because specific instructions which is recited on the printed matter is not set forth in the instant disclosure for any method, it is unclear what the printed material recites, and thus, the administration into a lumen is being interpreted as an intended use, and the instructions provided are being interpreted as the guidance necessary for handling and use of the reagent. (It is noted that claim 54 is not included in the basis of this rejection because it indicates that the printed material specifically instructs for the administration into a lumen which the Pierce Catalog & Handbook does not specifically teach.)

The Pierce Catalog & Handbook teaches sulfosuccimidyl 2-(biotinamido) ethyl-1,3-dithiopropionate (NHS-SS Biotin) which is a reagent comprising (a) a sulfo-NHS ester moiety ; (b) a biotin binding domain; and (c) dithiopropionate (product number 21331; page T-131). Additionally, the Pierce Catalog & Handbook provides the necessary guidance for use of this reagent and related reagents for use in cross linking experiments and a citation of references illustrating the use of the various compounds (pages T-155 through T-200). Further, Pierce provides and teaches methods for use of this reagent in the isolation of proteins present on the cell surface of a cell (see page T-127; summarized in fig 5b). The Pierce Catalog & Handbook provides both the reagents and kits, and the general guidance and instruction for use of each of these in the purification of a protein present on the surface of a cell, and thus, anticipates the kit set forth in claims 52 and 53.

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Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-11, 13, 16-30, 32 and 36-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over De La Fuente *et al.* (IDS reference), Hastie *et al.* (IDS ref.), and Rothschild *et al.* (US Patent 5,948,624) and the Pierce Catalog & Handbook, 1994-95.

Independent claims 1 and 55 are drawn to labeling a molecule exposed on the luminal surface of a cell *in situ* or *in vivo* and claims 19 and 51 are drawn to isolating a organ/tissue-specific molecule comprising the steps of providing a impermeable reagent to a cell wherein the reagent is comprises the three domains: (a) a sulfo-NHS ester moiety ; (b) a biotin binding domain; and (c) dithiopropionate. In the case of the methods of isolation, the labeled molecule is isolated by virtue of labeling domain, *i.e.* biotin-avidin binding. Dependent claims recite

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particular luminal spaces, such as specific tissues and organs, and types of cells present in said spaces, such as epithelial cells.

At the time of the claimed invention De La Fuente *et al.* teach the identification and isolation of molecules which are specific to pulmonary tissue in both normal and hypoxic rat lungs. Hastie *et al.* teach the identification of components in the respiratory tract of cow tracheae. In each case De La Fuente *et al.* and Hastie *et al.* teach to use NHS-LC-biotin for the identification and isolation of the particular components from the perfusible space within an organ and on a tissue, however they do not teach to use a cleavable NHS-SS-biotin heterobifunctional cross-liner as presently claimed. Rothschild *et al.* provide a more general description of heterobifunctional crosslinkers and for their use for the detection and isolation of biomolecules to identify and detect specific conjugates associated with a tissue that can be further used in determining the role of the molecule in the detection of disease or disorders. Each of these references teach at the time of the claimed invention, the identification of biomolecules on the cell surface could be detected and isolated using bi-functional cross-linkers was known and used in the art. However, none of the references specifically teach to use a cleavable cross-linker. At the time of filing, cleavable cross-linkers were known and used for the identification of molecules on the surface of a cell. The Pierce Catalog provides a listing of such compounds including NHS-LC-biotin and NHS-SS-biotin. The Pierce Handbook teaches that the use of a cleavable linker provides for the reversible biotinylation of a protein or peptide, specifically for the identification, isolation and detection of a molecule of interest, then for removal of the biotin the

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-SS- bond can be cleaved for purification of the protein from the biotin (see page T-131).

Unlike the NHS-LC-biotin which maintains biotinilated protien, the NHS-SS-biotin can be cleaved either for purification off a column or for the isolation of the purified protien absent the biotin modification. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the specific methods of De La Fuente *et al.* and Hastie *et al.* (IDS ref.), or those more general disclosed by Rothschild *et al.* with the cleavable cross-linkers for sale and discussed in the Pierce Catalog & Handbook. One having ordinary skill in the art would have been motivated to use the cleavable crosslinkers taught in the Pierce Catalog because of the ability to remove biotin from the protein of interest once it is isolated or in conjugation with other kits sold by Pierce for the labeling and isolation of biotinylated molecules (for example Immunopure avidin kit, page T-128). There would have been a reasonable expectation of success given the results of all De La Fuente *et al.*, Hastie *et al.* (IDS ref.), and Rothschild *et al.* and the general guidance and large number of citations provided by the Pierce Catalog & Handbook to successfully identify and isolate a organ/tissue-specific molecule comprising with a impermeable reagent to a cell wherein the reagent is comprises the three domains: (a) a sulfo-NHS ester moiety ; (b) a biotin binding domain; and (c) dithiopropionate.

Therefore, absent evidence to the contrary, the claims are *prima facie* obvious.

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Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Pauline Farrier whose telephone number is (703)305-3550.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

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